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Mesothelioma and Asbestos

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Key words: mesothelioma; amosite, grunerite, taconite, crocidolite, tremolite, anthophyllite. Winchite; risk estimation; etiology

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Abstract

The current state of knowledge concerning mesothelioma risk estimates is reviewed. Estimates of the risk of mesothelioma exist for the commercial asbestos fiber types chrysotile, amosite and crocidolite. Data also exist on which to assess risks for winchite (sodic tremolite) and anthophyllite asbestos. Uncertainty in estimates is primarily related to limitations in measurements of exposure. Differences in the dimensions of the various fiber types and of the same fiber types at different stages of processing add a further complication. Never-the-less, in practical terms, crocidolite presents the highest asbestos related mesothelioma risk. The risk associated with sodic tremolite (winchite) appears to be similar.

In chrysotile miners and millers, the mesothelioma risk has been linked with exposure to asbestiform tremolite. Exposure to chrysotile in a pure form seems likely to present a very low if any risk of mesothelioma. While the majority of mesothelial tumors result from exposure to the asbestos minerals, there are other well established and suspected etiological agents.

While a practical threshold seems to exist for exposure to chrysotile, it is unlikely to exist for the amphibole asbestos minerals, especially for crocidolite. To date there is no indication of an increased risk of mesothelioma resulting from non-commercial fiber exposure in the Taconite industry.

1. Introduction

While there had been isolated reports of primary malignant mesothelial tumours since at least the 18th century, the link between asbestos exposure and mesothelioma was not established until 1960 when Wagner et al. (1960) published their classic paper on the occurrence of this tumour in persons working and living in the vicinity of crocidolite (blue asbestos) mines in Cape province, South Africa. Since that time, research has examined the relationship between this tumour and other asbestos fiber types, certain naturally occurring non-asbestos fibers (eg: erionite, fluoroedenite), certain synthetic fibers (eg: vitreous fibers) and to a limited extent potential non-fiber etiological factors (eg: therapeutic radiation, SV40).

In order to estimate the risk of mesothelioma for workers and the general public, mathematical models have been developed and the risk of mesothelioma associated with each commercial asbestos fiber type estimated. In this paper, we will attempt to answer the questions what are the causes of mesothelioma, is fiber type important, what are the levels of risk, is there a threshold and is there evidence of an increased risk of mesothelioma in taconite miners?

2. Epidemiologically Established Causes of

There is little doubt that the amphiboles amosite, crocidolite, anthophyllite and "tremolite" asbestos fibers are associated with increased risks of mesothelioma (Table 1). While it seems clear that chrysotile contaminated with tremolite at the same levels as encountered in the Quebec chrysotile mines and mills is capable of increasing the risk of mesothelioma, the potential of "pure" chrysotile to induce mesothelioma in humans is still open to debate.

2.1. *Crocidolite*

Since the first report by Wagner et al. (1960), increased risks of mesothelioma have been demonstrated in Australian crocidolite miners and millers (Armstrong et al. 1988), in manufacturers of crocidolite filters for cigarettes (Talcott et al., 1989), in crocidolite gas mask workers (McDonald & McDonald. 1978; Acheson et al., 1982) and in crocidolite railroad brake manufacturers (Berry & Newhouse, 1983) among others. The potency of crocidolite is high with a "little crocidolite going a long way."

2.2. *Amosite*

Amosite (fibrous grunerite) has been linked to an increased risk of mesothelioma, but, remains a curiosity in that the risk in mining appears to be much lower (Sluis-Cremer et al., 1992) than appears to be the case in downstream manufacturing industries (Seidman et al., 1986; Acheson et al.,1984). However, this may be follow-up period, difficulties of ascertainment in South Africa or fiber dimension changes with processing.

2.3. *Anthophyllite*

Anthophyllite has been shown to increase mesothelioma risk, but the risk appears to be far less than with the other amphibole fibers (Table 1).

2.4. *Tremolite*

In a vermiculite mine in Montana, the mineral winchite, which is soda tremolite, has been linked with a high risk of mesothelioma (McDonald et al., 2002; 2004). The carcinogenic potency (for mesothelioma) of this asbestiform mineral from the Montana vermiculite mine appears to be similar to the potency of crocidolite (McDonald et al., 2002; 2004).

2.5. *Chrysotile*

There is little doubt that the mesothelioma risk is elevated in Quebec chrysotile miners and millers (McDonald et al., 1997), but this increased risk is associated with mines where workers were also exposed to asbestiform tremolite (Rowlands et al., 1982; McDonald and

McDonald, 1995). The likelihood that the mesothelial tumours are related to tremolite fiber exposure is supported by the extremely low rates of mesothelioma in downstream chrysotile only industries where asbestiform tremolite exposure would be expected to be much lower than encountered by the Quebec miners and millers (Gibbs, 2001).

2.6. *Non-Asbestos fibrous minerals*

Mesothelioma has now been shown to be associated with exposure to erionite, a fibrous zeolite (Baris et al., 1987; Wagner et al., 1985) and there is evidence that the tumour is also associated with exposure to the fibrous fluoredenite amphibole (Comba et al., 2003).

3. Experimental production of mesothelioma

Experimentally, many fibers with appropriate dimensions and biopersistence have been shown to be capable of producing mesothelioma. For example, it is now reasonably well established that synthetic vitreous fibers which are respirable, biopersistent and of certain dimensions, can induce mesothelioma (Stanton, 1983; Stanton & Wrench, 1972; Stanton et al., 1977; Davis, 1991; Pott and Roller, 1996). However, the evidence, to date has not shown increased risks of mesothelioma in workers exposed to synthetic vitreous fibers. Other fibers of sufficient biopersistence, if they are respirable, long and thin are also capable of inducing primary malignant mesothelial tumours in experimental animals.

4. Suspected causes of mesothelioma in humans

While there have been several agents postulated as responsible for mesothelioma, they remain to date as suspected links. Therapeutic radiation, on anecdotal evidence seems highly likely to be an occasional cause of mesothelioma (Hoffman et al., 1994), although the limited studies that have been done to date have not supported the association. There is some evidence that thorotrast treatment increases the risk of mesothelioma (Anderson et al., 1995). The virus SV40 has been shown to be capable of inducing mesothelioma experimentally (Carbone et al., 1999) and fragments of DNA from this virus reported in mesothelioma tumour (Gibbs et al ,.1998). In spite of claims of synergy with asbestos exposure there is as yet no evidence that the SV40 virus is responsible for mesothelioma in humans. However, research to establish whether or not it does have a role continues. There are also several chemicals including potassium borate, plutonium, beryllium and 2:6 dichloro benzonitrile that have been shown experimentally to induce mesotheliomas or are suspected of being capable of causing mesothelioma (Kurakawa et al.,1983; Sanders, 1992; Oels et al., 1971; Donna et al., 1991; Gold & Kathren, 1988).

5. The risk of mesothelioma by fiber-type

There is now little doubt that there are significant differences in the risk of mesothelioma associated with the various asbestos fibers. An indication of the order of magnitude of likely differences was evidenced by the very large differences in the proportional mortality of mesothelioma in various industries using various fiber types (Table 1). A criticism that can be justifiably levelled at proportional mortality ratios (PMRs), as in the case of mesothelioma, is that they increase steeply with increasing length of follow-up. Hence, comparisons must be made at similar periods since first exposure. A further complication is that exposure level influences risk and PMRs. One way to overcome these criticisms is to relate risk to level of estimated exposure as done by Darnton and Hodgson (2000). They produced models to estimate risk which were non-linear.

5.1. *Crocidolite, amosite and chrysotile*

The risks associated with these fiber types as reported by Darnton and Hodgson (2000) are shown in Table 2. The experiences of workers in other industries shown in Table 1 are supportive of these findings.

5.2. *Tremolite asbestos*

Hodgson and Darnton did not estimate the risk associated with asbestiform tremolite or with winchite. However, as shown in Table 1, McDonald et al. 2002 reported 285 deaths in a cohort of 406 vermiculite miners and 12 mesotheliomas for a PMR of 4.12%. The cohort of workers was exposed to an average concentration of 18 f/cc (McDonald et al., 2002).

5.3. *Chrysotile*

The risk estimates based on Hodgson and Darnton are shown in Table 2. In this table, all the studies are of workers with known exposure to chrysotile only (with the exception of the Carolina textile plant where crocidolite yarn was used for some years and the Balengero mine where it has been reported (Gruber ,1999) that some crocidolite was milled. Recently it has been suggested that crocidolite may have played a role in the occurrence of mesothelioma in chrysotile miners from Thetford Mines, Quebec (Egilman, 2003). In fact, there is good evidence that this was not the case, as studies of the lung tissue of workers from the Thetford Mines area have not shown the presence of crocidolite, only chrysotile and tremolite (McDonald et al., 1997). This is not the result of an analytical problem as crocidolite was found in the lungs of workers at Asbestos where crocidolite was used in a factory (McDonald et al.,1997). As the claimed source of the crocidolite is a riebeckite granite at one mine only, it would not explain the distribution of the mesotheliomas described by McDonald and McDonald (1995) as the mine in question would have been in the peripheral lower risk of mesothelioma mines.

It can be seen from Table 2 that the mesothelioma risks in the chrysotile mining industry are very different from those in the crocidolite mining industries. Indeed, many of the chrysotile studies had an expected mesothelioma mortality of zero. The total expected number of mesotheliomas based on the Hodgson and Darnton (2000) approach, but eliminating all studies in which crocidolite was a potential issue was less than 0.0009 per f/ml-year. If we further consider the evidence put forth by McDonald and McDonald (1995) that the mesothelioma risks are higher in the mines with tremolite exposure (demonstrated by tissue burden studies) the findings would suggest that “pure” chrysotile (ie: tremolite free) would pose an even lower risk.

Based on their analysis, Hodgson and Darnton report that the relative potency for causing mesothelioma by the commercial asbestos types, crocidolite, amosite and chrysotile is in the ratio of 500:100:1 respectively. This estimate assumes that the commercial chrysotile may be contaminated by tremolite.

6. Estimates of Risk

Camus et al., (1998) reported a study of women living in two chrysotile asbestos mining areas in Quebec, over the period 1970 to 1989. The average cumulative exposure was estimated as 25 fibers/ml years, with a plausible range from 5 to 125 fibers/ml years, equivalent to 105 fibers/ml working yrs, after converting to the measure used for occupational exposure over 40 hours a week.

Based on the EPA model of risk for mesothelioma, Camus et al. (2002) predicted that there should be 150 (range 30-750) mesothelioma in the Town of Asbestos. In fact there was 1 peritoneal mesothelioma. Based on the same model, 500 (range 500-2500) mesotheliomas were predicted to occur in the town of Thetford Mines. In fact 10 pleural mesothelioma were found. These models of prediction were based on risk parameters derived from mixed asbestos fiber type exposures and were clearly wrong. Based on the risk of 0.0009 /f/ml-years from Hodgson and Darnton (2000), the relative risk of mesothelioma, assuming linearity in this range would have been (1+0.0009 cum exp) = 1.09. Therefore the number of mesothelioma that would have been predicted in Thetford Mines would have been 9 deaths and at Asbestos would have been just less than 1 which is quite close to the observed numbers. Clearly the EPA model is incorrect and the Hodgson and Darnton estimates much closer to reality.

6.1. Uncertainties

Unfortunately, as with virtually all studies involving humans, there are uncertainties. The main uncertainties relate to the exposure estimates which of necessity often depend on extrapolation into the past. It has been necessary to convert measurements made with midget impingers (Gibbs and LaChance, 1974) and thermal precipitators (HEI-AR 1991) to membrane filter phase contrast microscopy equivalents with the associated limitations on the conversions. The shape of the relationship between mesothelioma and asbestos exposures at very low doses is also subject to some debate.

In spite of the limitations, it can be seen in Tables 1 and 2 that there is a fair degree of consistency in the risk estimates for the various fiber types.

6.2. Threshold of Risk

It is scientifically impossible to prove the negative. Never-the less, the evidence does exist that supports the existence of at least a practical threshold, that is a level at which for practical purposes the risk of mesothelioma is undetectable (Browne and Gibbs, 1998). In addition to the studies in which the risks were 0 in Table 2, there are several other studies where there is no evidence of chrysotile related mesothelioma (Table 1). Berry and Newhouse (1983) and Newhouse and Sullivan (1989) found no chrysotile related mesothelioma in a study involving friction product manufacturing workers followed from 1946 to 1986. The study clearly found crocidolite-related mesothelioma even though crocidolite had only been used for two short periods at the plant to manufacture railroad brakes. Studies of automobile brake mechanics (Table 3) show no increased risk of mesothelioma in studies in the USA, Spain, Germany and Canada. Further the UK proportional mortality study by Hodgson et al. (1997) shows no increased risk of mesothelioma in garage mechanics (PMR approx 0.33). Registry studies in

Scandinavia (Malker et al., 1985; Jarvholm & Brisman, 1988) also failed to show any increased risks. It has been claimed that the experience of brake mechanics in Australia demonstrates an increased risk (Leigh and Driscoll, 2003), but to date a systematic controlled study has not been carried out. The postulated increased risk is based on a series of cases from the Australian Mesothelioma Register. This contains extensive details on cases over about a 20-year period but, like most cancer registries, it does not have details on a comparison group of those without mesothelioma. This limits the conclusions that can be drawn.

Wong (2001) carried out a meta-analysis on the studies in Table 3 and found an overall RR of 0.90 (CI 0.66 - 1.23). While this does not reach significance, the consistency of the independent studies from various countries is highly significant statistically. The meta-analysis of Wong may perhaps be criticized on the grounds that in some of the studies the comparison was of vehicle mechanics compared to not being a vehicle mechanic that is the risk is relative to the average risk over all other occupations, including some occupations with a high mesothelioma risk. However, for three of the six studies (McDonald, Teschke, Agudo) there is an analysis that excludes those who had exposure to asbestos in high-risk occupations, and so this criticism is certainly invalid as far as these three studies are concerned. For the other three studies more information is necessary to be definite either way. If the analysis was restricted to the former three studies, the combined estimate would be 0.80 with 95% confidence interval of 0.44 to 1.49. The combined estimate does not rule out a small increased risk but does rule out a large increase in risk.

The absence of a single mesothelioma in workers employed for less than 2 years in the Quebec asbestos mining industry where exposures were high is indicative of a threshold. In that industry, out of a total cohort of about 11,000 men born 1891-1921, 8000 had died by 1992, so the pattern of results is unlikely to change significantly.

Another argument that might be made concerning a threshold for asbestos relates to fiber size. The International Agency for Research on Cancer did not classify attapulgite with fibers of length less than 5μm in length as carcinogenic. Studies by Stanton & Wrench (1972); Stanton (1973), Stanton et al. (1977) and Stanton & Layard (1978) showed that fibers greater than 8μm in length and less than 0.25 um in diameter had a higher probability of producing tumours than did shorter and larger diameter fibers. They also demonstrated that reducing the length of fibers by pulverization decreases the carcinogenicity as far as mesothelial tumour production is concerned. They concluded that pulverized blue asbestos of length less than 1.25-3.75μm could be discounted in mesothelioma production.

6.3. Pleural vs. Peritoneal Mesothelioma

In the study of chrysotile miners and millers in Quebec, there were 38 cases of mesothelioma, none of which was a primary peritoneal mesothelioma and only one of which invaded the peritoneum. In other chrysotile only industries, peritoneal mesothelioma rarely if ever occur. Thus, it appears that chrysotile may not cause peritoneal mesotheliomas. This would be quite consistent with the observation that mesotheliomas in the mining industry are related to asbestiform tremolite exposure. A very large exposure to chrysotile contaminated with chrysotile would be necessary to give adequate tremolite exposure to increase the pleural mesothelioma risk. Further analysis shows that the ratio of the slopes for peritoneal and pleural mesotheliomas is between 2.4 and 3.2, with the risks of peritoneal mesothelioma and pleural mesothelioma being identical at 90f/ml-yr for crocidolite and 55 f/ml-year for amosite (Hodgson & Darnton, 2000). This means that at lower concentrations, there is a predominance of pleural mesothelioma with peritoneal mesotheliomas occurring more frequently only when the exposure is higher. In the chrysotile mines, the tremolite as a contaminant is rarely if ever adequate to cause the peritoneal mesothelioma.

7. Predicting Incidence

The risk of mesothelioma depends on the nature of the fiber to which the person is exposed (fiber type and dimensions), duration of exposure, time since first exposure, age at exposure and rate of elimination of fibers from the lung. It is now reasonably well established that the risk of mesothelioma increases with time since first exposure to the power of 3 to 4. Equations expressing the relationship between mesothelioma incidence and exposure level, exposure duration and time since first exposure have been derived and can even take into account the rate of elimination of fibers from the body as shown below (Berry, 1999). This depends on the constants k which has been developed, based on various studies by various authors. The simple model is shown below (a). The models taking account of elimination are shown in (b and c).

a. Simple model.

$I(t) = KC\ [t^{3.2} – (t\text{-}d)^{3.2}]$ where $t>d$.
K = constant. C= fiber concentration; t = time since start of exposure; d=duration of exposure. (Hughes 1989)

b. Elimination model

$I\ (T) = ce^{-L(T-w)}(T\text{-}w)^3$ for $T>w$.

I(T) = Incidence at time T; c = afd where a is a constant; f is the fiber concentration and d = duration of exposure. L = elimination rate. T = time since the start of exposure and w is a lag period. (Berry 1999).

c. Simplified elimination model

$I\ (T) = ce^{-LT}\ T^3$.

I(T) = Incidence at time T; c = afd where a is a constant; f is the fiber concentration and d = duration of exposure. L = elimination rate. T = time since the start of exposure
(Berry 1999).

8. Taconite Mining

The studies that have been conducted in the Taconite Mining industry are shown in Table 4. The table includes the results of studies conducted at the Homestake Mine where workers were exposed to non-asbestiform cummingtonite grunerite. There were three studies at this mine (McDonald et al., 1978; Steenland et al. ,1995, Gillam et al., 1976; Brown et al., 1986) but a single case of mesothelioma, not considered to be associated with the mining exposure was reported in only one of the studies (McDonald et al., 1978). That study included persons with more than 20 years of service, so there was definitely adequate latency to detect mesothelioma. While the study by Higgins might be criticised for inadequate latency, the studies by Cooper et al. (1988, 1992) did allow an adequate time from first exposure to permit the detection of mesothelioma. To date there is no evidence of an increased risk of mesothelioma associated with taconite exposure.

A recent study by Brunner et al. (2007) found that between 1984 and 1998 there were 17 cases of mesothelioma that had ever worked as a taconite miner in Minnesota. All but one had had exposure to commercial asbestos.

9. Conclusions

Risk estimates exist for each of the main asbestos fiber types. The main limitation in these estimates is the measurements of exposure. There are large differences in mesothelioma risks associated with the different fiber types and it seems probable that chrysotile in a pure form may not cause mesothelioma in humans. Because, experimental evidence suggests that different lengths of fibers pose different mesothelioma risks, comparisons should be done on a size basis, but in practice such comparisons are not possible. However, it is possible that some of the differences in risk between industries using the same fiber type may be due to differences in fiber dimensions. A practical threshold seems to exist for exposure to chrysotile, but is unlikely for amphiboles.

Existing Taconite studies are limited for evaluation of mesothelioma risks, but to date does not suggest any increased risk of mesothelioma resulting from exposure to non-commercial fibers or cleavage fragments encountered in this industry.

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Table 1: Mesothelioma in various cohorts†

STUDY	TOTAL COHORT	DEAD	NUMBER OF CASES AND PROPORTIONAL MORTALITY
CROCIDOLITE			
Gas Mask manufacture Canada (McDonald & McDonald (1978)	199	56 (28%)	9 (16.1%)
Gas Mask Manufacture (Acheson et al. ,1982)	757	219 (28.9%)	5 (2.3%)
Mining Blue Asbestos – Australia (Berry et al., 2004)	6,908	2549 (36.9%)	231 (9.1%)
Mining Blue Asbestos - South Africa (Sluis-Cremer et al.,1992)	3,430	423 (12.3%)	20 (4.7%)
Blue Asbestos Cigarette filter Production (Talcott et al., 1989)	35	28 (80%)	5 (17.8%
AMOSITE			
Amosite Factory (Seidman et al., 1979)	820	528 (64.4%)	14 (2.7%)
Amosite factory UK (Acheson et al., 1984)	5,969	422 (7.1%)	5 (1.2%)
Mining Amosite Asbestos - South Africa (Sluis-Cremer et al.,1992)	3,212	648 (20.2%)	4 (0.6%)
Amosite factory - Tyler Texas – US (Levin et al., 1998)	1,130	315 (27.9%)	6 (1.9%)
MIXED FIBER TYPES			
Insulation workers – NY - New Jersey (Selikoff et al., 1979)	632	478 (75.6%)	38 (7.9%)
Insulators in shipyards – Sweden (Jarvholm & Sanden 1998)	248	86 (34.7)	7 (8.1%)
Insulation workers - US & Canada (Selikoff & Seidman 1991)	17800	4951 (27.8%)	458 (9.2%)
Dockyards UK	6292	1043 (16.6%)	31 (3.0%)
Insulators in shipyards – USA (Selikoff et al. 1979)	440	79 (17.9%	8 (10.1%)
Asbestos factory workers in London – UK (Newhouse & Berry 1979)	M 4,600	775 (16.8%)	46 (5.9%)
	F 992	225 (22.7%)	21 (9.3%)
TREMOLITE			
Vermiculite mining – USA (McDonald et al., 2002; 2004)	406	285 (70.2%)	12 (4.2%)
ANTHOPHYLLITE			
Anthophyllite miners –Finland (Karjalainen et al. 1994)	999	503 (50.3%	4 (0.8%)
Anthophyllite miners –Finland (Meurman et al., 1994)	735	137 (18.6%)	4 (2.9%)
CHRYSOTILE			
Chrysotile miners & millers (McDonald et al., 1997)	Total 9,780	8,009 (81.9%)	38 (0.47%)
	Thetford 5041	4125	25 (0.61%)
	Asbestos4031	3331	8 (0.2%)
	Factory 708	553	5 (0.9%)
Chrysotile Mining chrysotile Italy (Piolatto 1990)	1,058	427 (40.4%)	2 (0.46) Amphibole fibers have been milled at this mine.
Chrysotile textile plant (Dement et al., 1994)	3,022	1,259 (41.7%	2 (0.16%)
Chrysotile products factory (Weiss 1977)	264	66 (25%)	0
Asbestos cement plant (Thomas et al., 1982)	1,970	351	0

		(17.8%)	
Chrysotile Gas Mask Filter Workers (Acheson et al., 1982)	570	177 (31.1%)	1This case was also considered to have been exposed to blue asbestos at another factory. There was also an excess number of persons with cancer of the ovary at the blue fiber plant. These were considered by the authors to possibly be additional mesotheliomas.
Friction materials manufacture – USA (McDonald et al., 1984)	3,641	1,267 (34.7%)	0
Friction materials manufacture – UK (Newhouse & Sullivan 1989)	13,450	2577 (19.2%)	0 (There were 13 mesotheliomas in total ; 11 had contact with crocidolite; Of the two working with chrysotile, 1 diagnosis uncertain, 1 work history was not well established)

†Not all studies are independent as some involve overlaps and others follow-up of the same or very similar cohorts. The results of the latest follow-up are shown.

Table 2: Risk of mesothelioma per fiber/ml-year as reported by Hodgson & Darnton 2000(Adjusted for age at first exposure).

CROCIDOLITE	Percentage total expected mortality per f/ml-year
Massachusetts	0.68
Wittenoom	0.48
South Africa Crocidolite Mines	0.59
TOTAL CROCIDOLITE	0.51
AMOSITE	
Paterson	0.12
South Africa Amosite Mines	0.06
TOTAL AMOSITE	0.10
CHRYSOTILE	
Carolina (Men)!	0.0130
Balangero!	0.0025
Quebec	0.0009
Carolina (Women)	0
New Orleans	0
Connecticut	0
TOTAL CHRYSOTILE	0.0010 (<0.0009)*

* Excluding industries where some crocidolite used.

TABLE 3: Studies of friction product repair workers (from Wong et al. 2001) showing no increased risk of mesothelioma

STUDY	RELATIVE RISK
US Garage workers (McDonald et al.)	0.9 (0.39-2.13
Canada (Teschke et al.)	0.8 (0.20-2.30)
US Connecticut (Teta et al.)	0.65 (0.08-5.52)
Germany (Woitowitz & Rodelsperger)	0.87 (0.46-1.64)
Spain (Agudo et a.l)	0.62 (0.17-2.25)
US (Spirtas)	1.00 (0.90-1.60)

Table 4: Mortality from mesothelioma in workers exposed to Cummingtonite-Grunerite and "Fibers" in Taconite mines.

STUDY	DEATHS	MESOTHELIOMA
*Homestake (McDonald et al. 1978)	631	1 (Did not work in mine; dubious pathology + other exposures)
*Homestake Gold Miners (Steenland & Brown 1996)	1551	0
Reserve (Higgins et al. 1983)	298	0
**Two taconite mines (Cooper et al. 1992).	1058	1 (pleural) – Taconite exposure began only 11 years before death.

- * These cohorts have some overlap so cannot be considered as independent studies.
- ** There were two follow-up periods. Results for latest follow-up shown.